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(54) Title: EXTENDED-RELEASE FORM OF DILTIAZEM			
<p>(57) Abstract</p> <p>An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.</p>			

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## EXTENDED RELEASE FORM OF DILTIAZEM

## FIELD OF INVENTION

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

## BACKGROUND OF THE INVENTION

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension, either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in humans is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-release Diltiazem known under the

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trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Patent 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not 5 eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 10 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and 15 methylene chloride, which are dangerous to use due to their flammability and/or toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product 20 which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the 25 concomitant intake of food, and, further, which can be made by a process not using organic solvents.

#### SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with 30 extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become 35 more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which

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comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or 5 copolymer, and a pharmaceutically acceptable adjuvant.

Thus, according to one embodiment of the invention an extended-release galenical composition comprises beads comprising:

- a) an effective amount of said one or more 10 Diltiazem salts as an active ingredient, and
- b) a wetting agent, wherein said wetting agent comprises a sugar, C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and 15 polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous 20 membrane of an aqueous dispersion of a water-soluble or water-dispersible polymer or copolymer, for example a [ ] neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant. ]

According to another embodiment a pharmaceutical 25 composition is provided, comprising in capsule form an effective amount of one or more pharmaceutically acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and 30 polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

35 wherein said beads are coated with a microporous membrane of an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a

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pharmaceutically acceptable adjuvant, and one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

5 According to another aspect of the invention a method of treating angina pectoris or hypertension or both in a mammal is provided which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof and a wetting agent in the form of beads, wherein the wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an 10 ester of polyoxyethylene sorbitan, a glyceride-polyglycide, 15 an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein the beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral 20 copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant.

According to another aspect of the invention, the extended-release galenical formulation is adapted to release Diltiazem in 900 ml of water when USP XXII, apparatus no. 2 25 is used at 100 rpm, at a rate in the order of:

between about 5% and about 20% after 2 hours, for example 9% after two hours (in one embodiment with 5% after 1 hour);

between about 20% and about 50% after four hours, 30 for example 33-34% after four hours;

between about 30% and about 70% after six hours, for example 54% after 6 hours; and

between about 50% and about 90% after 8 hours, for example, between about 62% and about 82% after 8 hours.

35 Thus, according to another aspect of the invention an extended-release galenical composition is provided comprising beads containing:

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a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or 5 xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

10 wherein said beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP 15 XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

9% after 2 hours,

33% after 4 hours,

54% after 6 hours, and

20 between 62% and 83% after 8 hours.

#### BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be illustrated with respect to the following drawings illustrating embodiments of the invention in which:

25 Figure 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration 30 twice daily.

Figure 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is 35 taken with food.

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DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE  
INVENTION

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethyl-amino)ethyl]-2,3-dihydro-2, (4-methoxyphenyl)-1,5-  
5 benzothiazepin-4(5H) has been known for more than 20 years.  
The synthesis thereof is described in German patent  
1,805,714, corresponding to U.S. patent 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentration peaks, so that it is now possible to maintain diltiazem plasmatic concentration in a desired, effective range while simplifying the administration of the  
15 medicine to only once daily.

According to the present invention, the Diltiazem extended-release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem  
20 as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a  
25 pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts.  
30 However, they may also include the acetate, citrate or lactate salts, for example. It is preferred, however, that the hydrochloride salt be used.

In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is  
35 constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be the active substance. These galenic forms afford

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excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine  
 5 to only once daily.

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 20 However, they may also include the acetate, citrate or lactate salts, for example. It is preferred, however, that the hydrochloride salt be used.

In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is  
 25 constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance-containing beads are  
 30 presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:  
 35

sugars, for example saccharose, mannitol, sorbitol and lactose;

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- lecithins;  
 $C_{12}$  to  $C_{20}$  fatty acid esters of saccharose,  
 commercialized under the name of sucroesters  
 (Gattefosse, France) or under the name of crodesters (Croda,  
 5 U.K.);  
 xylose esters or xylites;  
 polyoxyethylenic glycerides;  
 esters of fatty acids and polyoxyethylene (Brijs,  
 Renex and Eumulgines, Henkel, RFA);  
 10 sorbitan fatty acid esters (Span, Atlas, U.S.A.);  
 polyglycides-glycerides and polyglycides-alcohols  
 esters (Gelucires, Gattefosse, France).  
 In addition to at least one of the above-named  
 wetting agents, the beads may contain excipients or  
 15 carriers, such as:  
 Microcrystalline celluloses, such as Avicel  
 products (FMC, U.S.A.); methylcelluloses,  
 carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol,  
 Hercules, U.S.A.), hydroxypropyl celluloses (Klucels,  
 20 Hercules, U.S.A.); and starches.  
 Among the water-soluble and/or dispersible film-  
 forming polymers or copolymers constituting the microporous  
 membrane, may be mentioned particularly polyacrylates and  
 polymethacrylates of the Eudragit type, such as Eudragit  
 25 E30D, L30D, RS - 30 D of Röhm Pharm (RFA), ethylcelluloses,  
 such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC,  
 U.S.A., Hydroxypropyl cellulose and hydroxypropyl-  
 methylcellulose and their derivations.  
 These polymers or copolymers may be associated  
 30 into the microporous membrane with at least one adjuvant as  
 exemplified by the following:  
 plastifying agents, such as triacetin,  
 dibutylphthalate, dibutylsebacate, citric acid  
 esters, polyethyleneglycols, polypropyleneglycols  
 35 and polyvinylpyrrolidone;  
 pigments, such as iron oxides and titanium oxide;  
 fillers, such as lactose and sucrose;

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wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

5

lubricants, such as magnesium stearate and talc;

10

antifoaming agents, such as silicone oil.

15

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

20

The weight of the microporous membranes may be 2 to 35%, preferably, 5 to 22% of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

25

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

30

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

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The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder for ALEXANDER WERK (RFA) or the apparatus 5 called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) 10 type is used.

15 Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting 20 agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

25 The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

30 A pasty or plastic mixture, appropriate to be granulated by means of any one of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

35 20 to 85% Diltiazem hydrochloride  
 2 to 20% sucroesters WE 15 (wetting agent);  
 5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);  
 2 TO 10% Methocel E 5 (hydroxypropyl-

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methylcellulose of DOW, U.S.A.);  
 1 to 15% polyvinylpyrrolidone and  
 5 to 40% distilled water.

Said microporous membrane may be applied onto said  
 5 beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or  
 10 fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient; however, in general, from about 120 mg to about 480  
 15 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt,  
 20 provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as  $\beta$ -adrenoceptor blocking agents or diuretics may be used in the present compositions. However,  
 25 these are only examples and are not intended to be limitative.

As examples of  $\beta$ -adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example..

30 As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide may be used, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired; however,  
 35 they need not be.

The present invention will now be further illustrated by reference to certain examples which are

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provided solely for purposes of illustration and are not intended to be limitative.

According to an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

- 10 to 70 Eudragit E30D (polymer)
- 0.5 to 15% talc (lubricant)
- 0.5 to 15% Titanium dioxide (lubricant)
- 10 0.5 to 15% Magnesium stearate (lubricant)
- 0.5 to 15% polyvinylpyrrolidone (plastifying agent)
- 0.01 to 2% silicone oil (antifoaming agent);
- 0.05 to 5% polysorbate 80 (wetting agent)
- 15 10 to 70% water (carrier)

#### EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended-release galenic forms, a process for preparing the same, therapeutic applications thereof and pharmacokinetic controls using the present galenic forms.

##### Example 1 - beads manufacture

30	Diltiazem hydrochloride	1120 g
	Lactose	119 g
	Microcrystalline cellulose (Avicel pH 101)	140 g
	Povidone K. 30	21 g

After introducing the powders into a planetary mixer and granulating with water, the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwerk). The small cylinders are rounded, so as to

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obtain beads, by means of a spheronizer. After drying at 60°C for 12 hours, the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

5

Example 2

	Diltiazem Hydrochloride	560 g
	Crodesta F 160	59.5 g
10	Microcrystalline cellulose (Avicel pH 101)	70 g
	Povidone K 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 minutes. 15 Thereafter, 100 ml water USP is added and the mixing is pursued for 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spaghetti". A spheronizer type caleva is used so as to 20 transform the extruded product into beads. After drying for 12 hours on trays in an oven at 60°C, the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm.

The amount of beads obtained with size comprised 25 between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a 30 STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technique. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter, the coated beads were dried at 50°C during 16 hours.

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## Coating suspension composition:

	Magnesium stearate	12.5 g
	Titanium dioxide	5.0 g
	Povidone k 30	5.0 g
5	Eudragit NE30D	620.0 g
	Talc USP	17.5 g
	water	338.0 g
	Simethicone	1.0 g
	Tween 80	0.8 g

10

"In vitro" dissolutions were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate buffer of 5.8 pH and a revolution speed of 100 rpm.

15

	<u>elapsed time [h]</u>	<u>percent dissolved [%]</u>
	1	5
	4	34
	8	62
20	12	84

Example 4

The beads, as in Example 2, were coated using a 25 fluidized bed coater equipped with "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30 - 35 g per minute. Thereafter, the coated beads were dried for 15 hours at 45°C.

30

## Coating suspension:

	Magnesium stearate	0.636 kg
	Talc	0.636 kg
	Titanium dioxide	0.0909 kg
35	Hydroxypropylmethylcellulose	0.200 kg
	Polysorbate 80 NF	0.007 kg
	Simethicone c emulsion	0.018 kg

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Eudragit NE 30 D	12.4	kg
purified water	6.7	kg

Dissolution "in vitro"

5       The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained at 37 ± 0.5°C

	<u>elapsed time [h]</u>	<u>percent dissolved [%]</u>
10	2	9
	4	33
	6	54
	8	82

Pharmacokinetical results

15     The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Patent 4,721,619 (Cardizem SR®). Therefore, 6 healthy subjects received successively in a random order 300 mg of each of 20 the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily, while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) for 7 days. On each of the eight days, 11 samples of blood were withdrawn when the product of 25 Example 4 was administered and 15 blood samples were withdrawn after the Cardizem SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. Figure 1 shows the results obtained: the continuous line represents the Diltiazem 30 plasma levels obtained with the product of Example 4 and the broken line, the Diltiazem plasma levels of Cardizem SR®.

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Figure 1

## 5 Pharmacokinetical parameters:

	Units	Example 4	Cardizem SR®
10	Area under the curve [0-24h]	mg.h/ml	2782 ± 1037 2864 ± 1222
15	Maximal concentration	mg/ml	116.3 ± 54.1 192.7 ± 85.3
20	Time of maximum concentration	h	8.0 ± 1.8 5.2 ± 2.8
25	Fluctuation	%	85.7 ± 25.7 109.5 ± 25
	Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3 6.7 ± 3.7

From these results, the following conclusion can be drawn:

Firstly, Fig. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Secondly, the bioavailability expressed by the areas under the curve of the 2 products is equivalent (no statistical detectable difference).

Thirdly, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizem SR® after a twice daily administration.

Fourthly, the time that the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with the product of the previous art when given twice daily.

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Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after a single oral dose of 300 mg given with and without food.

5 The clinical trial was conducted as an open, single dose, randomized, cross-over study. Blood samples were obtained before and up until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment during an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. 10 Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of 15 bioequivalence. Figure 2 curves show the mean plasma levels obtained when the product is taken without food and the dotted curve, the mean plasma levels obtained when the product is taken with food.

20

Figure 2

## Pharmacokinetics parameter - product of Example 4

	Units	Fasting	Food
25	Area under the curve (total)	mg.h/ml	1988 ± 119
30	Mean residence time	h	21.3 ± 0.7
35	K <sub>a</sub>	h <sup>-1</sup>	0.283 ± 0.024
	Maximum concentration	mg/ml	100 ± 4.8
			112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the 40 administration without food to within less than 20%, regarding the area under the curve, mean residence time and maximum concentration. The larger interval obtained for K<sub>a</sub>

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was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.4%).

From all the results, it appears clearly that the 5 product of the present invention can be administered once a day and that the plasma concentration variations are lower than the ones obtained with the conventional product given twice a day.

Having described the present invention, it will 10 now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

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THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing an effective amount of said one or more Diltiazem salts as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.  
5
2. The extended-release galenical composition of Claim 1, wherein said salt is the hydrochloride salt.  
15
3. The extended-release galenical composition of Claim 1, wherein said water-soluble or water-dispersible polymer is a polymer of acrylic acid methyl ester and acrylic acid ethyl ester or a copolymer of both.  
20
4. The extended-release galenical composition of Claim 1, wherein said wetting agent comprises a sugar, C<sub>12</sub> to C<sub>20</sub>, fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, glyceride-polyglycides, alcohol-polyglycide esters or lecithins or any combination thereof.  
25
- 30 5. The extended-release galenical composition of Claim 1, wherein the weight of the microporous membrane is about 4 to 35% by wt. of that of the uncoated beads.
- 35 6. A pharmaceutical composition containing an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises:

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- a) beads containing an effective amount of one or more pharmaceutically acceptable salts of Diltiazem and a wetting agent, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant, and
- b) one or more other pharmaceutically active ingredients which pharmaceutically active ingredients are pharmaceutically compatible with said one or more Diltiazem salts.

7. The pharmaceutical composition of Claim 6, wherein said one or more other pharmaceutically active ingredients comprises  $\beta$ -adrenoceptor or diuretic compounds or compositions containing the same.

8. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

9. The method of Claim 8, wherein said administration is orally and once per day.

10. The method of Claim 8, wherein said mammal is a human.

11. The method of Claim 9, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts in total are administered per day.

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12. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads, said beads comprising:
- a) an effective amount of said one or more 5 Diltiazem salts as an active ingredient, and
  - b) a wetting agent, wherein said wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and 10 polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,
- wherein said beads are coated with a microporous 15 membrane of at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.
13. The extended-release galenical composition of 20 Claim 12, wherein said salt is the hydrochloride salt.
14. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads. 25
15. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.
16. The extended-release galenical composition of Claim 12, wherein the water-soluble or water-dispersible polymer or copolymer comprises an aqueous dispersion or a neutral copolymer or ethyl acrylate and methyl methacrylate. 30
17. A pharmaceutical composition comprising an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which 35

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comprises in capsule form,

beads comprising an effective amount of one or more pharmaceutically-acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar,  
5 a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or  
10 any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

15 one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

18. The pharmaceutical composition of Claim 17,  
20 wherein said one or more other pharmaceutically active ingredients comprises β-adrenoceptor or diuretic compounds or compositions containing the same.

19. The pharmaceutical composition of Claim 17,  
25 wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

20. The pharmaceutical composition of Claim 17,  
wherein said salt is the hydrochloride salt.

30 21. The pharmaceutical composition of Claim 17,  
wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

35 22. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an

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- extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads and a wetting agent, wherein the wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or 5 xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination 10 thereof, wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.
- 15 23. The method of Claim 22, wherein said administration is orally and once per day.
24. The method of Claim 22, wherein said mammal is a human.
- 20 25. The method of Claim 23, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts are administered in total per day.
- 25 26. The method of Claim 22, wherein said salt is the hydrochloride salt.
27. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, 30 which comprises beads containing:
- a) an effective amount of said one or more Diltiazem salts as an active ingredient, and
  - b) a wetting agent, wherein the wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or 35 xylose, a glyceride of sucrose, a fatty acid of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of

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polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof, wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

10           9% after 2 hours,  
               33% after 4 hours,  
               54% after 6 hours, and  
               between 62% and 82% after 8 hours.

15 28.       The extended-release galenical composition of Claim 27, wherein said salt is the hydrochloride salt.

20 29.       The extended-release galenical composition of Claim 27, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

30 30.       The extended-release galenical composition of Claim 29, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

25 31.       An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing:

30           a) an effective amount of said one or more Diltiazem salts as an active ingredient, and  
               b) a wetting agent, wherein the wetting agent comprises a sugar, a C<sub>12</sub>-C<sub>20</sub> fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

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wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane 5 is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no 2. is used at 100 rpm, at a rate on the order of:

- 10            between 5% and 20% after 2 hours,  
              between 20% and 50% after 4 hours,  
              between 30% and 70% after 6 hours, and  
              between 50% and 90% after 8 hours.

32.          The extended-release galenical composition of Claim 31, wherein said salt is the hydrochloride salt.

15          33.          The extended-release galenical composition of Claim 31, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

20          34.          The extended-release galenical composition of Claim 33, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

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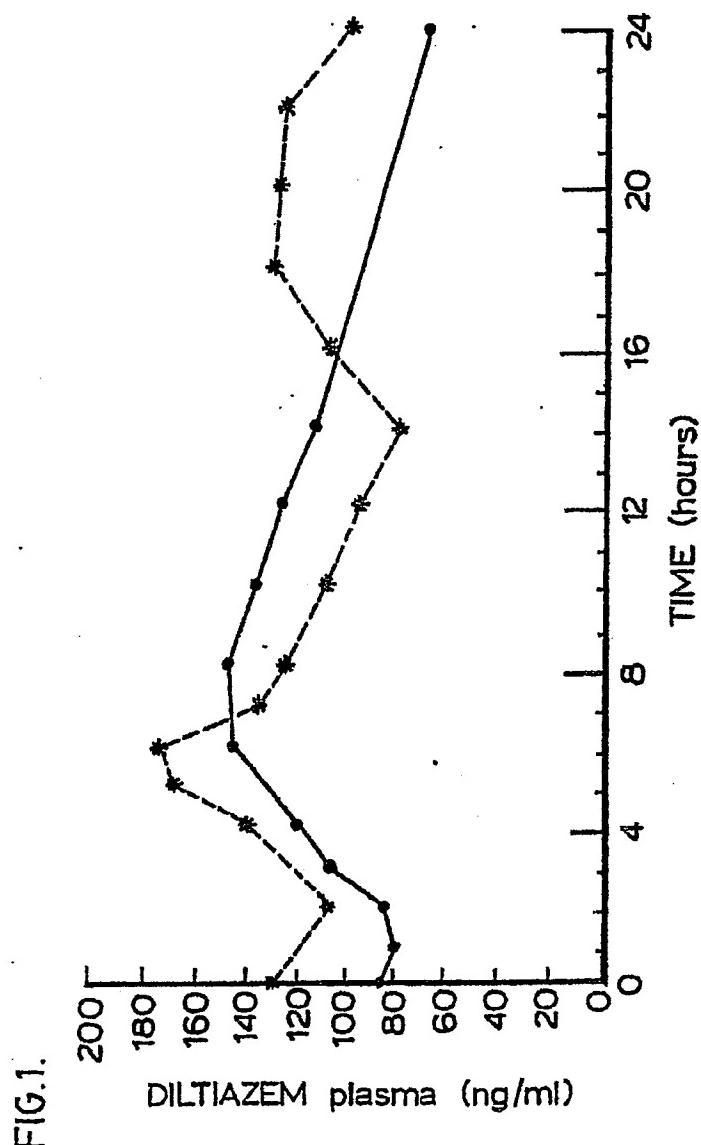


FIG.1.

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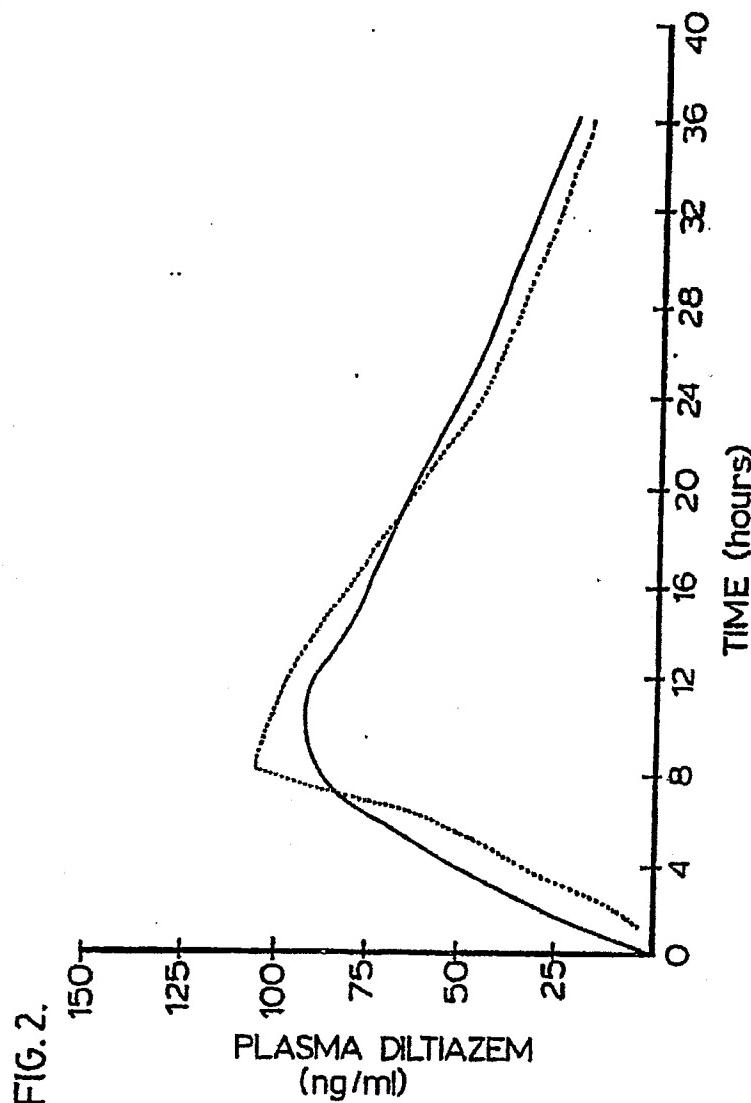


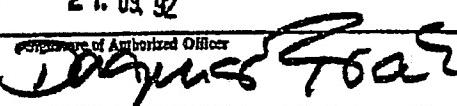
FIG. 2.

SUBSTITUTE SHEET

A-621

## INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 92/00290

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>1</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5 A 61 K 31/55 A 61 K 9/52 A 61 K 9/54		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>2</sup>		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>3</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>4</sup></b>		
Category <sup>5</sup>	Citation of Document, <sup>6</sup> if with indication, where appropriate, of the relevant passages <sup>7</sup>	Relevant to Claim No. <sup>8</sup>
A	EP,A,0373417 (SCHERING) 20 June 1990, see the claims; page 3, lines 25-53; page 4, lines 21-32	1-3, 12- 13, 16- 17, 20, 27-28, 31-32
A	EP,A,0340105 (SANOFI) 2 November 1989, see the claims; column 2, lines 9-31; column 3, lines 4-23, 46-53	1-3, 12- 13, 16- 17, 20, 27-28, 31-32
A	EP,A,0322277 (SYNTHELABO) 28 June 1989, see the claims; column 1, lines 23-52; column 2, lines 23-29	1-3, 12- 13, 16- 17, 20, 27-28, 31-32
	-----	-/-
<p><sup>1</sup> Special categories of cited documents:  <sup>2</sup> "A" document defining the general state of the art which is not considered to be of particular relevance  <sup>3</sup> "C" earlier document but published on or after the international filing date  <sup>4</sup> "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reasons (as specified)  <sup>5</sup> "O" document referring to an oral disclosure, etc., exhibition or other means  <sup>6</sup> "P" document published prior to the international filing date but later than the priority date claimed  <sup>7</sup> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  <sup>8</sup> "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step  <sup>9</sup> "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art  <sup>10</sup> "Z" document member of the same patent family       </p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search 01-09-1992	Date of Mailing of this International Search Report 21.09.92	
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer 	

Form PCT/ISA/230 (second sheet) (January 1985)

Mme Dagmar FRANK

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Page 2

ALL DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0149920 (ELAN) 31 July 1985, see the claims; page 4, lines 26-35 (cited in the application)	1-4

Form PCT/ISA/210 (second sheet) (January 1985)

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

CA 9200290  
SA 61640

This annex lists the patent family members relating to the patent documents cited in the above-mentioned International search report.  
The members are as contained in the European Patent Office EPO file on 16/09/92  
The European Patent Office is in no way liable for those particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0373417	20-06-90	AU-A-	4664889	26-06-90
		CA-A-	2004565	31-05-90
		WO-A-	9006107	14-06-90
EP-A- 0340105	02-11-89	FR-A-	2630647	03-11-89
		AU-B-	614056	15-08-91
		AU-A-	3336389	02-11-89
		DE-U-	6890090	09-04-92
		JP-A-	1313431	18-12-89
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		AU-A-	2707788	22-06-89
		DE-A-	3868037	05-03-92
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		US-A-	5112621	12-05-92
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		CH-A-	662507	15-10-87
		DE-A-	3485023	10-10-91
		JP-A-	50156617	16-08-85
		US-A-	4891230	02-01-90
		US-A-	4917899	17-04-90
		US-A-	4894240	16-01-90
		US-A-	4721619	26-01-88

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

EPO FORM P07

**D**

**A-625**

BIOVAI LABORATORIES INC.  
Cardizem NT, 120, 180, 240, 300, 360 and 420 mg

Amendment to a Pending New Drug Application  
NDA #21-392

### **SECTION 3 – CHEMISTRY, MANUFACTURING AND CONTROLS**

#### **PART II – Drug Product**

##### **B. Quantitative Composition – continued**

<b>Component</b>	<b>Cardizem NT</b>	<b>120 mg</b>	<b>180 mg</b>	<b>240 mg</b>	<b>300 mg</b>	<b>360 mg</b>	<b>420 mg</b>
	<b>% w/w</b>	<b>mg/tab</b>	<b>mg/tab</b>	<b>mg/tab</b>	<b>mg/tab</b>	<b>mg/tab</b>	<b>mg/tab</b>
<b>Diltiazem HCl Extended Release Coated Beads</b>							
Diltiazem Hydrochloride, USP	33.84	120.0	180.0	240.0	300.0	360.0	420.0
Microcrystalline Cellulose, USP	4.23	15.00	22.50	30.00	37.49	44.99	52.50
Povidone K30, USP	0.64	2.25	3.38	4.50	5.63	6.75	7.94
Sucrose Stearate	3.59	12.73	19.10	25.47	31.84	38.20	44.56
Magnesium Stearate, NF	0.38	1.34	2.00	2.67	3.34	4.00	4.67
Talc, USP	0.38	1.34	2.00	2.67	3.34	4.00	4.67
Titanium Dioxide, USP	0.11	0.38	0.57	0.76	0.95	1.14	1.33
Hydroxypropyl Methylcellulose 2910, USP	0.22	0.76	1.15	1.53	1.91	2.29	2.67
Polysorbate 80, NF	0.01	0.03	0.05	0.06	0.08	0.09	0.11
Simethicone C Emulsion, USP	0.01	0.02	0.04	0.05	0.06	0.07	0.08
Eudragit NE30D	4.41	15.63	23.45	31.26	39.08	46.89	54.70
Purified Water, USP	*	*	*	*	*	*	*
<b>Wax Placebo Beads</b>							
Microcrystalline Wax, NF	20.10	71.28	106.91	142.55	178.19	213.83	249.47
Pregelatinized Starch, NF	13.46	47.73	71.60	95.46	119.33	143.19	167.06
Sodium Starch Glycolate, NF	6.63	23.51	35.27	47.02	58.78	70.53	82.29
Croscarmellose Sodium, NF	2.88	10.21	15.32	20.43	25.53	30.64	35.74
Colloidal Silicon Dioxide, NF	0.48	1.70	2.55	3.40	4.26	5.11	5.96
Hydrogenated vegetable oil, Type I, NF	4.81	17.06	25.58	34.11	42.64	51.17	59.70
<b>Tablet Coating:</b>							
Opadry II White	3.84	13.62	20.43	27.23	34.04	40.85	47.66
Carnauba Wax, NF	0.01	0.03	0.05	0.07	0.09	0.11	0.12
<b>Theoretical Total Coated Tablet Weight</b>	<b>100.00</b>	<b>354.61</b>	<b>531.91</b>	<b>709.21</b>	<b>886.52</b>	<b>1063.83</b>	<b>1241.13</b>

\*Water used for the manufacture of the beads is evaporated during the manufacturing process. The water content of the beads is NMT 2.0%.

**E**

**A-627**

**Listing of Claims: Consolidating Subject Matter Claimed in  
Biovail '451 and '338 Patent Applications**

Claim 1 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem selected from the group consisting of Diltiazem and the pharmaceutically acceptable salts thereof, suitable for evening dosing every 24 hours the dosage comprising at least one bead comprising a core and at least one coating, the at least one bead being formulated in an oral dosage form containing from about 120 mg to about 540 mg of the form of Diltiazem, the Diltiazem in the core of each bead associated with excipients, the at least one coating covering the core comprising a water swellable and diffusible coating which permits hydration of the core by gastrointestinal fluids, the water swellable and diffusible coating comprising at least one lubricant and/or at least one hydrophilic polymer and a water insoluble swellable neutral copolymer, the at least one bead providing controlled (sustained) release of the form of Diltiazem and providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 after administration, the preparation comprising the form of Diltiazem in oral sustained-release dosage form in which the form of Diltiazem is adapted to be released after administration, over a prolonged period of time and

A) when given to humans exhibits the following properties:

(i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and

(ii) bioequivalence when given in the morning with and without food according to the same FDA guidelines or criteria; and

B) in vitro exhibits the following in vitro release characteristics;

(i) releases the diltiazem or a pharmaceutically acceptable salt thereof into a aqueous median at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

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- (b) between about 7% and about 35% after 4 hours;
- (c) between about 30% and about 58% after 8 hours;
- (d) between about 55% and about 80% after 14 hours;
- (e) in excess of about 75% after 24 hours;

and/or (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium"

- (a) between about 1% and about 25% after 2 hours;
- (b) between about 7% and about 45% after 4 hours;
- (c) between about 30% and about 68% after 8 hours;
- (e) in excess of about 75% after 24 hours.

Claim 2 (previously amended): The controlled release Galenical preparation of claim 1 wherein the neutral copolymer is selected from the group consisting of

- (i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer,
- (ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate, and
- (iii) a neutral copolymer without any functional groups that form water insoluble films and the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 5 (previously amended): The controlled-release Galenical preparation of claim 1 in which the form of Diltiazem is adapted to be control released after

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administration of the preparation over a period of time and is more preferably adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

- (a) between about 4% and about 8% after 2 hours;
- (b) between about 16% and about 21% after 4 hours;
- (c) between about 44% and about 52% after 8 hours;
- (d) between about 69% and about 76% after 14 hours; and
- (e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

- (a) between about 4% and about 15% after 2 hours;
- (b) between about 16% and about 30% after 4 hours;
- (c) between about 44% and about 62% after 8 hours;
- (d) in excess of about 80% after 24 hours.

Claim 6 (previously amended): The preparation of claim 4 wherein the Cmax of Diltiazem in the blood is obtained between about 11 - about 13 hours after administration of the preparation.

Claim 7 (previously amended): The preparation of claim 1, 2, 5 or 6 wherein the form of Diltiazem is in the form of Diltiazem HCl.

Claim 8 (previously amended): The preparation of claim 6 wherein the preparation is a diffusion controlled preparation.

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Claim 9 (previously amended): The preparation of claim 5 wherein the preparation releases the Diltiazem at a rate of less than about 15% of the total amount of active per hour during dissolution.

Claim 10 (previously amended): The preparation of claim 9 in capsule form.

Claim 11 (previously amended): The preparation of claim 9 in tablet form.

Claim 12 (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent.

Claim 13 (original): The preparation of claim 12 wherein the Diltiazem is mixed (in whole or in part) with the wetting agent.

Claim 14 (previously amended): The preparation of claim 13 wherein the wetting agent assists to maintain the solubility of the Diltiazem in each microgranule, ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein.

Claim 15 (previously amended): The preparation of claim 14 wherein the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

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Claim 16 (previously amended): The preparation of claim 12 wherein the preparation comprises a mixture of the Diltiazem and/or pharmaceutically acceptable salt with the wetting agent and the membrane comprises a water-dispersible or water-soluble polymer and a water-, acid- and base-insoluble polymer of a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester which hydrates the preparation.

Claim 17 (previously amended): The preparation of claim 16 wherein the membrane comprises a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester and hydroxypropylmethylcellulose.

Claim 18 (previously amended): The preparation of claim 17 wherein the membrane hydrates the core within a membrane which when put in gastrointestinal fluid causes the membrane to swell while fluid penetrates and hydrates the microgranule, and dissolves the diltiazem and wetting agent and benefits from a concentration gradient through the membrane (high concentration inside and low concentration outside).

Claim 19 (previously amended): The preparation of claim 13 wherein the Diltiazem is mixed with the wetting agent and the membrane comprises an acrylic membrane and plasticizer combined to form the membrane thereby providing a mechanism of release from this membrane which "washes" the diltiazem through pores created when the plasticizer incorporated in the membrane, is released in gastrointestinal fluid.

Claim 20 (previously amended): The preparation of claim 9 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof

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associated with any suitable dissolution agent (other than a wetting agent) to assist in the release of the Diltiazem from the preparation.

**Claim 21 (previously amended):** The preparation of claim 20 wherein the dissolution agent is an organic acid comprising adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid or tartaric acid which permits the diltiazem to dissolve in gastrointestinal fluids even when the microgranules pass into the regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

**Claim 22 (previously amended):** A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 1 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning, the method comprising administering to a patient in need thereof the preparation in the evening.

**Claim 23 (original):** A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 2 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

**Claim 24 (original):** A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 5 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

**Claim 25 (original):** A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 6

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to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 26 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 7 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 27 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 8 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 28 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 9 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 29 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 10 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 30 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 11 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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Claim 31 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 12 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 32 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 13 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 33 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 14 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 34 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 15 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 35 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 16 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 36 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 17 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

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Claim 37 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 18 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 38 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 19 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 39 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 20 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 40 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 21 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 41 (previously amended): The preparation of claim 1 wherein the preparation contains 120 mg of Diltiazem.

Claim 42 (previously amended): The preparation of claim 1 wherein the preparation contains 180 mg of Diltiazem.

Claim 43 (previously amended): The preparation of claim 1 wherein the preparation contains 240 mg of Diltiazem.

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Claim 44 (previously amended): The preparation of claim 1 wherein the preparation contains 300 mg of Diltiazem.

Claim 45 (previously amended): The preparation of claim 1 wherein the preparation contains 360 mg of Diltiazem.

Claim 46 (previously amended): The preparation of claim 1 wherein the preparation contains 420 mg of Diltiazem.

Claim 47 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 41, 42, 43, 44, 45 or 46 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 48 (previously amended): The preparation of claim 17 wherein the wetting agent is selected from:

sugars;  
saccharose, mannitol, sorbitol;  
lecithins;  
 $C_{12}$  to  $C_{20}$  fatty acid esters of saccarose;  
xylose esters or xylites;  
polyoxyethylenic glycerrides;  
esters of fatty acids and polyoxyethylene;  
sorbitan fatty acid ester;  
polyglycides-glycerides and polyglycides-alcohols esters  
Metal salts.

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Claim 49 (previously amended): The preparation of claim 12 wherein the wetting agent is in association with the diltiazem in the microgranule and not mixed therewith, the membrane comprises a water-soluble or water dispersible polymer or copolymer selected from the group consisting of hydroxypropylmethylcellulose and a water-, acid- and base-insoluble polymer which is a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester which enables the bead to be hydrated by the introduction of gastrointestinal fluids into the core hydrating the core and therefore mixing the diltiazem and the wetting agent.

Claim 50 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 48 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 51 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 49 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 52 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 1 which comprises the following constituents:

	% W/W
(a) Diltiazem hydrochloride	69 - 73
(b) Microcrystalline cellulose	8 - 9.5
(c) (Polyvinyl Pyrrolidone)	1 - 2
(d) Sucrose stearate	7 - 8
(e) Magnesium stearate NF	0.5 - 2.5

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(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing)

Claim 53 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 52 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 54 (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

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(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 55 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 54 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 56 (previously amended): The preparation of claim 12 in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

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(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 57 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 56 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 58 (previously amended): The preparation of claim 12 wherein the preparation is a tablet and the tablet comprises microgranules in association

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with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 59 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 58 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 60 (previously amended): The controlled-release Galenical preparation of claim 2 in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

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- (c) between 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;
- (d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and
- (e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 61 (original): The preparation of claim 60 wherein the microgranules are in capsule form.

Claim 62 (original): The preparation of claim 60 wherein the microgranules are in tablet form.

Claim 63 (previously amended): The preparation of claim 60 wherein the core and membrane comprise:

- (i) in the core,
  - (a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

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(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 64 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 1, which preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

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(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer such as hydroxypropylmethylcellulose; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants,

wherein the core and membrane comprise:

	% W/W
(a) Diltiazem hydrochloride	69 - 73
(b) Microcrystalline cellulose	8 - 9.5
(c) (Polyvinyl Pyrrolidone)	1 - 2
(d) Sucrose stearate	7 - 8

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(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	(Polyoxyethylene Sorbitan Monoleate)	0.01 - 0.025
(j)	Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

Claim 65 (previously amended): The preparation of claim 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 66 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 60 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claims 67-109 (cancelled)

Claim 110 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 1, wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or

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pharmaceutically acceptable salt thereof associated with a wetting agent,  
wherein the wetting agent is selected from:

sugars;  
saccharose, mannitol, sorbitol;  
lecithins;  
 $C_{12}$  to  $C_{20}$  fatty acid esters of saccharose;  
xylose esters or xylites;  
polyoxyethylenic glycerrides;  
esters of fatty acids and polyoxyethylene;  
sorbitan fatty acid esters;  
polyglycides-glycerides and polyglycides-alcohols esters  
Metal salts.

Claim 111 (cancelled)

Claim 112 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 110 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 113 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 111 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 114 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 4 wherein the preparation comprises a plurality of microgranules, each microgranule

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comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

	% W/W
(a) Diltiazem hydrochloride	69 - 73
(b) Microcrystalline cellulose	8 - 9.5
(c) (Polyvinyl Pyrrolidone)	1 - 2
(d) Sucrose stearate	7 - 8
(e) Magnesium stearate NF	0.5 - 2.5
(f) Talc USP	0.5 - 5.0
(g) Titanium dioxide (USP)	0.15 - 0.3
(h) Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j) Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k) neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
Purified water USP	0 (used for mixing)

Claim 115 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 112 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 116 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 5 wherein the preparation comprises a plurality of microgranules, each microgranule

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comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

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(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 117 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 116 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 118 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 5 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent, in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

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(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 119 (original): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 118 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claims 120-121 (cancelled)

Claim 122 (previously amended): A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem according to Claim 1 wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or

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pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

(d) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and

(e) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid

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methyl ester, together with suitable adjuvants which permits hydration of the core by gastrointestinal fluids.

Claim 123 (original): The preparation of claim 122 wherein the microgranules are in capsule form.

Claim 124 (original): The preparation of claim 122 wherein the microgranules are in tablet form.

Claim 125 (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with suitable adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 50% of the total preparation of lubricant selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative;

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- (d) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof; and
- (e) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with suitable adjuvants.

Claim 126 (previously amended): The preparation of claim 122, 123 or 124 wherein the core and membrane comprise:

	% W/W
(a) Diltiazem hydrochloride	69 - 73
(b) Microcrystalline cellulose	8 - 9.5
(c) (Polyvinyl Pyrrolidone)	1 - 2
(d) Sucrose stearate	7 - 8
(e) Magnesium stearate NF	0.5 - 2.5
(f) Talc USP	0.5 - 5.0
(g) Titanium dioxide (USP)	0.15 - 0.3
(h) Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i) (Polyoxyethylene Sorbitan Monooleate)	0.01 - 0.025
(j) Simethicone C emulsion USP (dry of 30%)	0.01 - 0.015
(k) a neutral acrylic polymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
Purified water USP	0 (used for mixing).

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Claim 127 (previously amended): The preparation of claim 122 or 124 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with suitable excipients and adjuvants.

Claim 128 (previously amended): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 122, 123 or 124 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 129 (previously added): The preparation of claim 110 wherein the neutral copolymer is selected from the group consisting of

- (i) a water-, acid-, and base-insoluble polymer of a neutral acrylic polymer;
- (ii) a neutral acrylic copolymer of ethyl acrylate and methyl methacrylate;
- (iii) a neutral copolymer without any functional groups that form water insoluble films; and

the lubricant is selected from the group consisting of: talc, magnesium stearate and a polyethylene glycol derivative and/or the hydrophilic polymer is selected from the group consisting of hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, povidone and any combination thereof.

Claim 130 (previously added): The preparation of claim 116, 118 and 122 wherein the lubricant is selected from the group consisting of talc, magnesium stearate and a polyethylene glycol derivative.

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Reply to Office Action

Claim 131 (previously added): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 129 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 132 (previously added): A method of treatment of a patient's hypertension and/or angina comprising the administration of the preparation of Diltiazem of claim 130 to the patient in the evening for effective treatment of the patient's hypertension and/or angina the next morning.

Claim 133 (New): The preparation of Claim 1 in capsule form.

Claim 134 (New): The preparation of Claim 1 in tablet form.

Claim 135 (New): The preparation of Claim 2 in capsule form.

Claim 136 (New): The preparation of Claim 2 in tablet form.

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not have deviated from the teachings of EPA '313 to use a neutral copolymer as there is no motivation provided by the teachings of EPA '313 to use a neutral copolymer.

The Examiner has recommended a side-by-side comparison of the EPA '313 formulation to that of Applicant's claimed formulation. Applicant has now compared pharmacokinetic parameters of the preparation as claimed in the instant application (currently marketed as Cardizem LA), which is limited to a neutral copolymer, to the product described in EPA '313 (see Tables 1 and 2 and Figures 1 and 2). EPA '313 is equivalent to US 5,002,776, which is listed in the FDA Orange Book for Cardizem CD. The pharmacokinetic data for Cardizem CD has been published in Thiffault et al. (previously submitted to the Examiner - should the Examiner require a copy of this reference, please advise):

Parameters	Table 1			
	<u>Cardizem LA 360 mg</u>		<u>Cardizem CD 240 mg*</u>	
	<u>Day</u>	<u>Night</u>	<u>Day</u>	<u>Night</u>
AUC <sub>0-τ</sub>	<u>3691 ± 1449</u>	<u>4251 ± 1219</u>	<u>2008 ± 814</u>	<u>1754 ± 715</u>
C <sub>max</sub>	<u>274.5 ± 149.0</u>	<u>290.9 ± 94.0</u>	<u>137.7 ± 48.6</u>	<u>127.6 ± 47.8</u>
Plasma Fluctuation	<u>118.9 ± 70.8</u>	<u>93.6 ± 29.5</u>	<u>112.5 ± 25.5</u>	<u>125.8 ± 31.2</u>

a - data based on Thiffault article

AUC<sub>0-τ</sub> = Steady-state area under the curve, τ = dosing interval = 24 hours

To normalize for the differences in dosage strength of the two diltiazem preparations, the above data is presented below in Table 2 as a Night/Day ratio:

Parameters	Night/Day Ratio	
	<u>Cardizem LA</u>	<u>Cardizem CD</u>
AUC	1.15	0.874
C <sub>max</sub>	1.06	0.927
Plasma Fluctuation	0.787	1.12

Table 1 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 1 is converted to Night/Day ratios of the pharmacokinetic parameters it is quite clear that the pharmacokinetics of LA is better than that of CD (Table 2). The LA formulation provides for a much higher bioavailability (both AUC and  $C_{max}$  are  $>$  than 1) and lower plasma fluctuation ( $< 1$ ) during the night than CD.

Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg

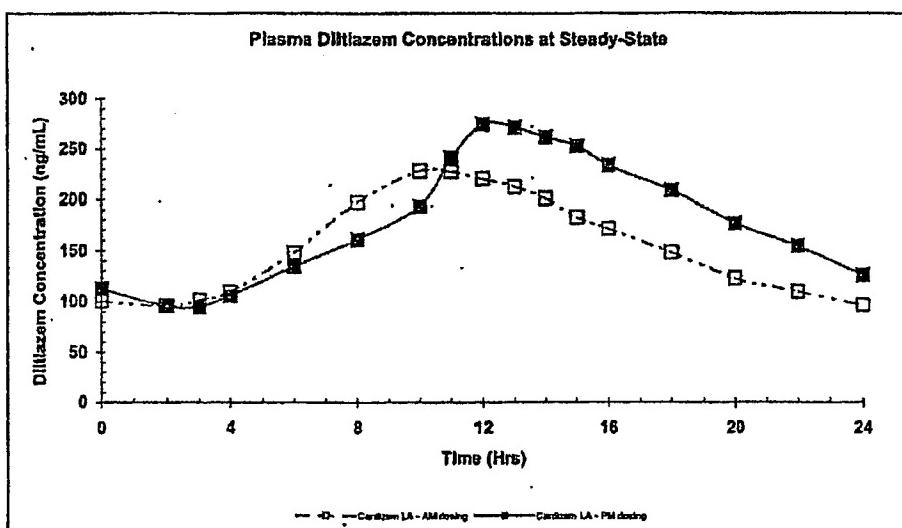
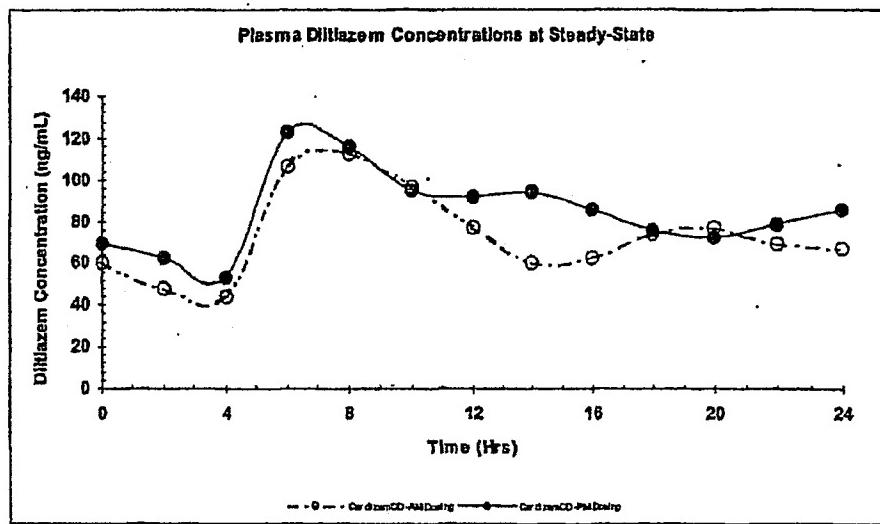


Figure 2: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem CD 240 mg



#### LA-PM vs. AM DOSING

Figure 1 together with Tables 1 and 2 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begins to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher  $C_{max}$  is reached when dosed in the evening (see also Tables 1 and 2),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 1 and 2, AUC Night/Day ratio >1). The higher

bioavailability of diltiazem from the LA formulation translates to higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to CD (see Table 2).

#### CD PM vs. AM DOSING

Figure 2 together with Tables 1 and 2 show that:

1. CD when dosed at night begins to increase around 4 hrs after administration and peaks about 6 hrs after administration. Thus, dosing CD around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower  $C_{max}$  is reached when dosed in the evening compared to LA (almost half of LA, see Figure 2 and Tables 1 and 2,  $C_{max}$  Night/Day ratio is < 1),
3. A lower bioavailability is achieved when dosing in the evening compared to LA (see Tables 1 and 2, AUC Night/Day ratio is < 1), CD exhibits much higher plasma fluctuation and hence more adverse effects compared to LA (see Table 2).

The above data clearly show the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer, compared to the product described by EPA '313, which teaches the use of charged copolymers of acrylic and methacrylic acid ester polymers and neither teaches nor suggests the use of a neutral copolymer. Further, EPA '313 neither teaches nor suggests the night-time effect of administering its product on the bioavailability of diltiazem. This effect would not be inherent to the EPA '313 product as the pharmacokinetics of the product disclosed in EPA '313 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected

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Applicant respectfully submits, one needs to recognize the problem, see, for example, *Monarch Knitting Machine Corporation v. Solzer Morat GmbH*, 45 USPQ 2d (1977), 1981-1982 (Fed. Cir. 1998)

"where the District Court's formulation of the problem confronting the '053 inventors presumes the solution to the problem - modification of the stem segment. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. See, EG *In re Antal*, 58 CCPA 1382 444 F.2d 1168, 1171-72, 170 USPQ 285, 287-88 (CCPA 1971)."

Therefore, again, Applicant respectfully submits WO '093 does not render obvious Applicant's invention. This is clearly shown in the data below where pharmacokinetic parameters of the preparation as claimed in the instant application currently marketed as Cardizem LA, which is limited to a neutral copolymer to the product described in WO '093 (see Tables 3 and 4 and Figures 1 and 3). WO '093 is equivalent to US 5,529,791, which is listed in the FDA Orange Book for Tiazac. Tiazac is not a chronotherapeutic product as clearly spelled out in Figure 8 of Applicant's application.

Parameters	<u>Cardizem LA 360 mg</u>		<u>Tiazac 360 mg<sup>b</sup></u>	
	<u>Day</u>	<u>Night</u>	<u>Day</u>	<u>Night</u>
AUC <sub>0-τ</sub>	3691 ± 1449	4251 ± 1219	2870 ± 1005	2754 ± 810
C <sub>max</sub>	274.5 ± 149.0	290.9 ± 94.0	243.2 ± 79.0	200.3 ± 59.1
Plasma Fluctuation	118.9 ± 70.8	93.6 ± 29.5	171.4 ± 43.8	144.8 ± 26.7

b - Data based on Bioclin Research Laboratories Analytical Report. Report is available should the Examiner request it.

AUC<sub>0-τ</sub> = Steady-state area under the curve, τ = dosing interval = 24 hours

Table 4 below provides night/day ratio

Parameters	Table 4	
	Cardizem LA	Tiazac
AUC	1.15	0.960
C <sub>max</sub>	1.06	0.824
Plasma Fluctuation	0.787	0.845

Table 3 shows the raw data for the various pertinent pharmacokinetic parameters. When the data in Table 3 is converted to night/day ratios of the pharmacokinetic parameters, it is quite clear that the pharmacokinetics of LA is better than that of Tiazac (Table 4). The LA formulation provides for a much higher bioavailability, both area under the curve and C<sub>max</sub> are greater than 1 and lower plasma fluctuation during the night than Tiazac.

For ease of reference and comparison, Figure 1 is re-produced below:

Figure 1: Mean Steady-State Diltiazem Concentrations Following Administration of Cardizem LA 360 mg

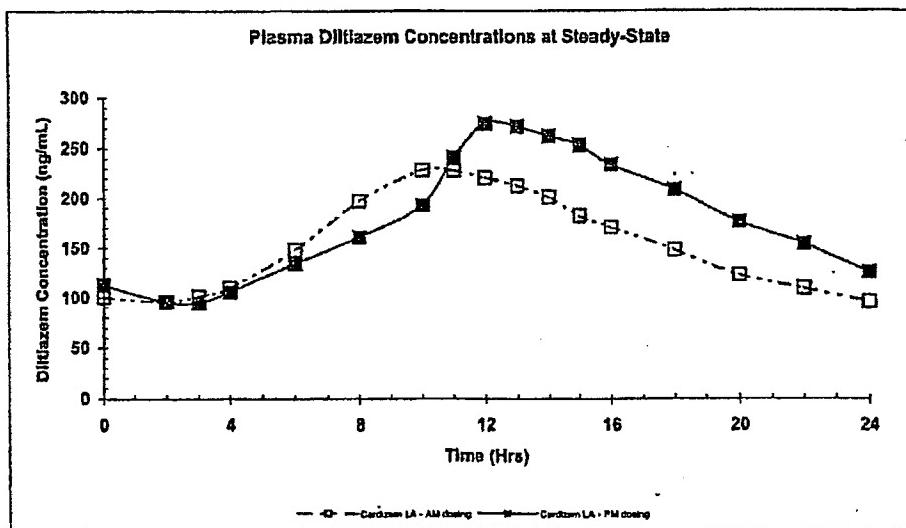
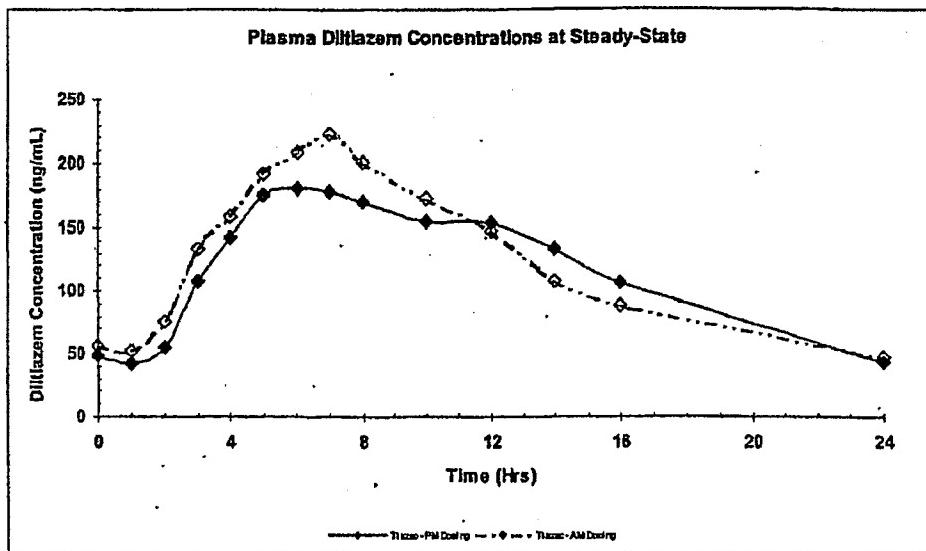


Figure 3: Mean Steady-State Diltiazem Concentrations Following Administration of Tiazac 360 mg.



#### LA-PM vs. AM DOSING

Figure 1 together with Tables 3 and 4 demonstrate that:

1. When dosed in the evening, plasma diltiazem concentrations begins to rise at about 4 hrs after administration and peaks at about 11 hrs. Keeping in mind the fact that epidemiological studies have shown that the greatest incidence of heart problems and sudden cardiac death occur during the early morning waking hours when blood pressure is rising in response to the natural circadian rhythm, administering LA around 8-10 pm would result in diltiazem levels peaking during the critical early morning waking hours when the drug would be needed most,
2. A higher  $C_{max}$  is reached when dosed in the evening (see also Tables 3 and 4),
3. The bioavailability of diltiazem is higher when LA is dosed in the evening (see Tables 3 and 4, AUC Night/Day ratio >1). The higher

bioavailability of diltiazem from the LA formulation translates to higher plasma diltiazem concentrations, and

4. LA exhibits a lower plasma fluctuation when compared to Tiazac (see Table 4).

#### TIAZAC PM vs. AM DOSING

Figure 3 together with Tables 3 and 4 show that:

1. Tiazac when dosed at night begins to increase around 2 hrs after administration and peaks at about 6 hrs after administration. Thus, dosing Tiazac around 8-10 pm would result in diltiazem levels peaking much too early (around 2-4 am),
2. A lower Cmax is reached when dosed in the evening compared to LA (see Figure 3 and Tables 3 and 4, Cmax Night/Day ratio is <1),
3. A lower bioavailability is achieved when dosed in the evening compared to LA (see Tables 3 and 4, AUC Night/Day ratio is <1),
4. Tiazac exhibits a higher plasma fluctuation and hence more adverse effects compared to LA (see Table 4).

The above data clearly shows the unexpected results obtained by the instantly claimed invention, which comprises the use of a neutral copolymer compared to the product described by WO '093. WO '093 does not teach or suggest a night time effect of administering its product on the bioavailability of diltiazem. Further, this effect would not be inherent to the WO '093 product as the pharmacokinetics of the product disclosed in WO '093 is significantly different from the product as claimed in the instant invention as established by the data above. All of the unexpected novel features of the instantly claimed invention result in the true chronotherapeutic formulation. Therefore, Applicant's invention clearly exhibits unexpected results. Furthermore, the above comparison, Applicant respectfully submits, addresses the Examiner's concern that the previous data submitted regarding Tiazac was

concerning a 240 mg formulation and the data regarding Applicant's claimed formulation was based on a 300 mg capsule. Now, the comparison to Tiazac, as well as to the Applicant's formulation, are now based on the same dosage amount, thus satisfying the Examiner's request.

Given the facts provided above, Applicant respectfully submits that the Examiner has failed to establish a *prima facie* case for obviousness in view of EPA '313 and in view of WO '093. Again, the Applicant refers the Examiner to the data presented above showing the unexpected results obtained when a neutral copolymer is used.

Applicant respectfully reminds the Examiner that the criteria for obviousness determinations are well established in US Patent Law and have been set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). To establish obviousness based on a combination of the elements disclosed in the prior art there must be some motivation suggested in their teaching of the desirability of making the specific combination that was made by the Applicant. See *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000), citing *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) and *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984).

While the Examiner asserts that "One of ordinary skill in the art would have been motivated to manipulate the formulation based on the specifics of the desired formulation", the Examiner has not provided any analysis regarding how any one of the references should be modified to arrive at the claimed invention. Rather, the Examiner provides the conclusory statement that it would have been obvious to one of ordinary skill in the art at the time of the invention to create a controlled release formulation of diltiazem based on the teachings of EPA '313 or WO '093 with the reasonable expectation of producing a composition that would exhibit Applicants'

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## Orange Book Detail Record Search

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Search results from the "OB\_Rx" table for query on "020062."

Active Ingredient: DILTIAZEM HYDROCHLORIDE  
 Dosage Form;Route: CAPSULE, EXTENDED RELEASE; ORAL  
 Proprietary Name: CARDIZEM CD  
 Applicant: BIOVAIL  
 Strength: 120MG  
 Application Number: 020062  
 Product Number: 001  
 Approval Date: Aug 10, 1992  
 Reference Listed Drug Yes  
 RX/OTC/DISCN: RX  
 TE Code: AB3

Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: DILTIAZEM HYDROCHLORIDE  
 Dosage Form;Route: CAPSULE, EXTENDED RELEASE; ORAL  
 Proprietary Name: CARDIZEM CD  
 Applicant: BIOVAIL  
 Strength: 180MG  
 Application Number: 020062  
 Product Number: 002  
 Approval Date: Dec 27, 1991  
 Reference Listed Drug Yes  
 RX/OTC/DISCN: RX  
 TE Code: AB3

Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: DILTIAZEM HYDROCHLORIDE  
 Dosage Form;Route: CAPSULE, EXTENDED RELEASE; ORAL  
 Proprietary Name: CARDIZEM CD  
 Applicant: BIOVAIL  
 Strength: 240MG  
 Application Number: 020062  
 Product Number: 003  
 Approval Date: Dec 27, 1991  
 Reference Listed Drug Yes  
 RX/OTC/DISCN: RX  
 TE Code: AB3

Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: DILTIAZEM HYDROCHLORIDE  
 Dosage Form;Route: CAPSULE, EXTENDED RELEASE; ORAL  
 Proprietary Name: CARDIZEM CD  
 Applicant: BIOVAIL  
 Strength: 300MG

## Orange Book Detail Record Search

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Application Number: 020062  
Product Number: 004  
Approval Date: Dec 27, 1991  
Reference Listed Drug Yes  
RX/OTC/DISCN: RX  
TE Code: AB3

Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: DILTIAZEM HYDROCHLORIDE  
Dosage Form;Route: CAPSULE, EXTENDED RELEASE; ORAL  
Proprietary Name: CARDIZEM CD  
Applicant: BIOVAIL  
Strength: 360MG  
Application Number: 020062  
Product Number: 005  
Approval Date: Aug 24, 1999  
Reference Listed Drug Yes  
RX/OTC/DISCN: RX  
TE Code: BC

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